

commonly assigned patent applications Pirrung *et al.*, U.S.S.N. 07/362,901 (VLSIPS parent) filed on June 7, 1989; and Pirrung *et al.*, U.S.S.N. 07/492,462 (VLSIPS CIP), filed on March 7, 1990 (now U.S. 5,143,854), which are hereby incorporated herein by reference. U.S.S.N. 09/577,875, filed April 24, 2000, is also a continuation-in-part of U.S.S.N. 08/348,471 filed November 30, 1994, which is a continuation of U.S.S.N. 07/805,727 filed December 6, 1991 (now U.S. 5,424,186), which is a continuation-in-part of U.S.S.N. 07/624,120, filed December 6, 1990, which is a continuation-in-part of U.S.S.N. 07/492,462, filed March 7, 1990 (now U.S. 5,143,854), which is a continuation-in-part of U.S.S.N. 07/362,901, filed June 7, 1989. Additional commonly assigned applications Barrett *et al.*, U.S.S.N. 07/435,316 (caged biotin parent) filed November 13, 1989; and Barrett *et al.*, U.S.S.N. 07/612,671 (caged biotin CIP), filed November 13, 1990 are also incorporated herein by reference. Additional applications Pirrung *et al.*, U.S.S.N. 07/624,120 (now abandoned) a divisional of which has issued as U.S. 5,744,101 and Dower *et al.*, U.S.S.N. 07/626,730 (now U.S. 5,547,839), which are also commonly assigned and filed on the same day as this application, are also hereby incorporated herein by reference.

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✓ Please replace the paragraph at page 12, line 12-13 with the following paragraph:

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Figs. 4A-4M illustrate the process of a VLSIPS™ Technology trinucleotide synthesis.

✓ Please replace the paragraph at page 18, lines 3-33 with the following paragraph:

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In the nucleic acid nucleotide sequencing application, a VLSIPS™ Technology substrate is synthesized having positionally defined oligonucleotide probes. See Pirrung *et al.* (1992) U.S. Pat. No. 5,143,854; and U.S. Patent No. 5,489,678. By use of masking technology and photosensitive synthetic subunits, the VLSIPS™ Technology apparatus allows for the stepwise synthesis of polymers according to a positionally defined matrix pattern. Each oligonucleotide probe will be synthesized at known and defined positional locations on the substrate. This forms a matrix pattern of known relationship between position and specificity of interaction. The VLSIPS™ Technology allows the production of a very large number of different oligonucleotide

10<sup>2</sup>, 10<sup>3</sup>, 10<sup>4</sup>, 10<sup>5</sup>, 10<sup>6</sup>, or even more, and at densities of at least about 10<sup>2</sup>/cm<sup>2</sup>, 10<sup>3</sup>/cm<sup>2</sup>, 10<sup>4</sup>/cm<sup>2</sup>, 10<sup>5</sup>/cm<sup>2</sup> and up to 10<sup>6</sup>/cm<sup>2</sup> or more. This application discloses methods for synthesizing polymers on a silicon or other suitably derivatized substrate, methods and chemistry for synthesizing specific types of biological polymers on those substrates, apparatus for scanning and detecting whether interaction has occurred at specific locations on the substrate, and various other technologies related to the use of a high density very large scale immobilized polymer substrate. In particular, sequencing, fingerprinting, and mapping applications are discussed herein in detail, though related technologies are described in US Pat. No. 5,489,678 and US Pat. No. 5,427,908, each of which is hereby incorporated herein by reference.

Please replace the paragraph at page 87, line 34 through page 88, line 2 with the following paragraph:

With a detection method selected, an apparatus for scanning the substrate will be designed. Apparatus as described in U.S.S.N. 07/362,901, from which CIP U.S.S.N. 07/492,462 issued as U.S. Pat. No. 5,143,854, and U.S. Patent No. 5,489,678 are particularly appropriate. Design modifications may also be incorporated therein.

Please replace the paragraph at page 89, lines 12-28 with the following paragraph:

The principle of the hybridization sequencing procedure is based, in part, upon the ability to determine overlaps of short segments. The VLSIPS™ Technology provides the ability to generate reagents which will saturate the possible short subsequence recognition possibilities. The principle is most easily illustrated by using a binary sequence, such as a sequence of zeros and ones. Once having illustrated the application to a binary alphabet, the principle may easily be understood to encompass three letter, four letter, five or more letter, and even 20 letter alphabets. A theoretical treatment of analysis of subsequence information, to reconstruction of a target sequence is provided, e.g., in Lysov, Yu., et al. (1988) Doklady Akademi. Nauk. SSR 303:1508-1511; Khrapko K., et al. (1989) FEBS Letters 256:118-122; Pevzner, P. (1989) J. of

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Biomolecular Structure and Dynamics 7:63-69; and Drmanac, R. et al. (1989) Genomics 4:114-128; each of which is hereby incorporated herein by reference.

< Please replace the paragraph at page 104, lines 16-31 with the following paragraph: >

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Although not described in detail here, but below for oligonucleotide probes, the VLSIPS™ Technology would typically use a photosensitive protective group on an oligonucleotide. Sample oligonucleotides are shown in Figure 1. In particular, the photoprotective group on the nucleotide molecules may be selected from a wide variety of positive light reactive groups preferably including nitro aromatic compounds such aso-nitrobenzyl derivatives or benzylsulfonyl. See, e.g., Gait (1984) Oligonucleotide Synthesis: A Practical Approach, IRL Press, Oxford, which is hereby incorporated herein by reference. In a preferred embodiment, 6-nitro-veratryl oxycarbonyl (NVOC), 2-nitrobenzyl oxycarbonyl (NBOC), or  $\alpha,\alpha$ -dimethyl-dimethoxybenzyl oxycarbonyl (DEZ) is used. Photoremovable protective groups are described in, e.g., Patchornik (1970) J. Amer. Chem. Soc. 92:6333- 6335; and Amit et al. (1974) J. Organic Chem. 39:192-196; each of which is hereby incorporated herein by reference.

< Please replace the paragraph at page 123, lines 7-17 with the following paragraph: >

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With the fingerprinting method as an identification means, problems arise from mosaicism in an organism. A mosaic organism is one whose genetic content in different cells is significantly different. Various clonal populations should have similar genetic fingerprints, though different clonal populations may have different genetic contents. See, for example, Suzuki et al. An Introduction to Genetic Analysis (4th Ed.), Freeman and Co., New York, which is hereby incorporated herein by reference. However, this problem should be a relatively rare problem and could be more carefully evaluated with greater experience using the fingerprinting methods.